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Contribution Of Vaccination And Treatment In Reduction Of Re-Infection Of Hbv Disease:A Mathematical Model Analysis And Numerical Simulation

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Abstract

Hepatitis B is a globally infectious disease. HBV-reinfection after HBV-related liver transplantation is a frequent clinical problem. The risk of HBV-reinfection directly correlates with the viral load before liver transplantation. If reinfection does occur in most cases the course of the disease is enhanced compared to the situation before transplantation. The progression of HBV-related liver disease is accelerated starting 2 months after transplantation and r in re-transplantation or death of the patients. Mathematical modeling of HBV transmission is an interesting research area. In this paper, we present characteristics of HBV virus transmission in the form of a mathematical model. We proposed and analyzed a compartmental nonlinear deterministic mathematical model SVEIRE for transmission dynamics and control of Hepatitis B virus disease. In this model, we used force infection which takes the contact rate of susceptible population and transmission probability into account. We proved that the solution of the considered dynamical system is positive and bounded. The model is studied qualitatively using the stability theory of differential equations and the basic reproductive number that represents the epidemic indicator is obtained from the largest eigenvalue of the next-generation matrix. Both local and global asymptotic stability conditions for disease-free and endemic equilibria are determined. Sensitive analysis results show that enhancing the vaccination rate for newborns and treatment for chronically infected individuals is very effective to stop the transmission of HBV. It is also shown that re-infection of HBV plays a great role in increasing the number of infected populations. Finally, this paper depicts combination of vaccination and treatment that will be the most useful way to control Hepatitis B virus infection.

Introduction

The hepatitis B virus (HBV) is a small, partially double-stranded DNA virus that causes acute and chronic hepatitis in humans. More than 350 million people are persistently infected, making HBV one of the most hazardous viral pathogens for humans and a global public health concern [1, 2]. Although universal vaccination being available for over three decades, an estimated 248 million persons are chronically infected with the hepatitis B virus (HBV) globally, constituting a major health burden.The prevalence of acute and chronic infection with hepatitis B virus (HBV) remains high worldwide.

Viral reinfection is the main problem after liver transplantation for hepatitis B virus (HBV)-related liver disease. Despite universal vaccination and antiviral therapies being available for decades, chronic hepatitis B (CHB) remains the leading primary liver disease for liver transplantation in many parts of the world.

Chronically infected individuals are at a risk of 15–25% of dying from HBV-related complications such as end-stage liver cirrhosis or hepatocellular carcinoma, accounting for over one million deaths annually [2, 3]. HBV-reinfection after HBV-related liver transplantation is a frequent clinical problem. The risk of HBV-reinfection directly correlates with the viral load before liver transplantation. If reinfection does occur in most cases the course of the disease is enhanced compared to the situation before transplantation [4]. The progression of HBV-related liver disease is accelerated starting 2 months after transplantation and resulting in re-transplantation or death of the patients. In the early 1990s, this observation resulted in the opinion of many transplant centers that liver transplantation for HBV-related liver disease might be a questionable indication. Earlier results demonstrated that HBV vaccination failure—especially after passive immunization with a monoclonal antibody—may be associated with the selection of mutants in the determinant and thus vaccination was no longer protective [5, 6]. Individuals with a history of HBV infection who receive immunosuppressive therapy are at risk for HBV reactivation and a flare of their HBV disease. This can result in increased serum

aminotransferase levels, fulminant hepatic failure, and/or death [2].Long-term antibody to hepatitis B surface antigen (anti-HBs) immunoprophylaxis (hepatitis B immune globulin [HBIG]) is an efficient way of preventing HBV reinfection in HBV DNA–negative patients. While the combination of Nucleos(t)ide Analogs (NAs) and passive immunization with hepatitis B immunoglobulins (HBIG) revolutionized the effective control of reinfection and replication, recent studies indicated NA monotherapy after Liver Transplantation for HBV-associated ESLD might be efficient with comparable outcomes in certain subgroups. Liver transplantation is not a sterilizing cure for CHB infection, therefore long-term antiviral prophylaxis is required. As the virus is never completely eradicated after transplant, the main goal of antiviral prophylaxis is to prevent reactivation, rather than recurrence or reinfection. Current available antiviral prophylaxis using nucleos(t)ide analogs (NAs) ± hepatitis B immunoglobulin (HBIG) are highly effective in preventing HBV reactivation after liver transplantation.

Mathematical models can be a useful tool in this approach which helps us to optimize the use of finite sources or simply to goal (the incidence of infection) control measures more impressively. Based upon these facts, we developed a mathematical model that takes vaccination, treatment and re-infection of HBV into account.

Model Description and Formulation

To analyze and control hepatitis B virus (HBV) infection in the present paper, we consider a model with two controls: vaccination and treatment. Firstly, in this study, two controlling variables are considered (vaccination and treatment) in order to prevent the spread of the HBV and finally to put down the infection from the population. We divided the population into five compartments namely: Susceptible S(t),Vaccination V(t),Exposed E(t), Infected I(t) and Recovered R(t).

Susceptible population increases by coming in of recruitment rate b and decreases by subsequently vaccinated population by the rate θ ,by force of infection entering exposed population and by natural death rate μ.Vaccinated population increases by the coming in of susceptible population who are subsequently vaccinated population by the rateθ and decreases by immunized population entering recovered compartment by the rate δ_2. The exposed population increase by the coming in of population from susceptible compartment by force of infection, by re-infection rate γ when recovered population make a contact with infected population of HBV and decreases by τ,probability of the individual entering I from E,force of infection, progression rate k from E to I and natural death rate μ. The infected population Increases by the coming in of τ,probability of the individual entering I from E,force of infection, progression rate k from E to I and decrease by natural recovery rate δ_1,treatment rate σ,HBV disease induced death rate d, and natural death rate μ. The recovered population increases by the coming in of natural recovery rate δ_1,treatment rate σ, immunized population by the rate δ_2 and decreases by re-infection rate γ and natural death rate μ. Force of infection $\lambda=\beta cI/N$ where:

β-Transmission probability

c- Contact rate of susceptible population with infective population

N- Total Population

Flow Chart of the Model

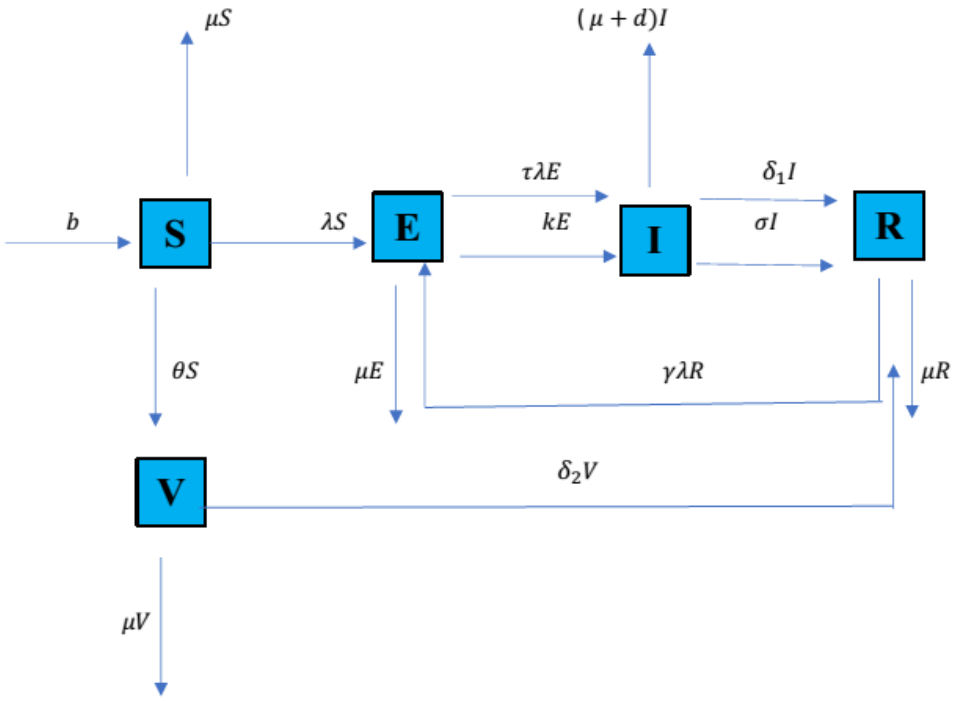

Figure 1: Flow chart of the model

Corresponding Dynamical system

$$\dot{S} = \quad b - (\theta + \mu + \lambda)S \tag{1}$$

$$\dot{V} = \theta S - (\delta_2 + \mu)V \tag{2}$$

$$\dot{E} = \lambda S + \gamma\lambda R - (\tau\lambda + k + \mu)E \tag{3}$$

$$\dot{I} = (\tau\lambda + k)E - (d + \delta_1 + \sigma + \mu)I \tag{4}$$

$$\dot{R} = (\delta_1 + \sigma)I + \delta_2 V - (\gamma\lambda + \mu)R \tag{5}$$

Mathematical Analysis of the Model

In this section, the positivity, boundedness, and existence of the solution of the model are checked. This mathematical analysis of the model could be considered as the primary result.

Theorem 1 (Positivity) Let the initial data for the model $S(0) = S_0 > 0, V(0) = V_0 > 0, E(0) = E_0 > 0, I(0) = I_0 > 0, R(0) = R_0 > 0$.

Proof

Let $S(0)=S_0 > 0$, $V(0)=V_0 > 0$, $E(0)=E_0 > 0$, $I(0)=I_0 > 0$, $R(0)=R_0 > 0$. Moreover, we assume that all parameters are positive. To show this, we take these differential equations of the dynamical system given above and show that their solutions are nonnegative as follows.

1.Let us take the first differential equation

$\dot{S} = b - (\theta + \mu + \lambda)S$. This implies $dS/dt = b - (\theta + \mu + \lambda)S$.

$dS/dt + (\theta + \mu + \lambda)S = b$

After solving using the technique of separation of variables and applying the initial conditions, the following is obtained:

$S(t) \geq S_0 e^{-(\theta+\mu+\lambda)t)}$. Since $S_0 > 0$ and $e^{-(\theta+\mu+\lambda)t}$ is also positive, then we can conclude that: $S(t) \geq S_0 e^{-(\theta+\mu+\lambda)t} > 0$.

2. Let us take the second differential equation

$\dot{V} = \theta S - (\delta_2 + \mu)V$. This implies $dV/dt = \theta S - (\delta_2+\mu)V$.

$dV/dt + (\delta_2 + \mu)V = \theta S$

After solving using the technique of separation of variables and applying the initial conditions, the following is obtained:

$V(t) \geq V_0 e^{-(\delta 2+\mu)t}$. Since $V_0 > 0$ and $e^{-(\delta 2+\mu)t}$ is also positive, then we can conclude that: $V(t) \geq V_0 e^{-(\delta 2+\mu)t} > 0$.

3.Let us consider the third differential equation

$\dot{E} = \lambda S + \gamma\lambda R - (\tau\lambda + k + \mu)E$. This implies $dE/dt = \lambda S + \gamma\lambda R - (\tau\lambda + k + \mu)E$.

After solving using the technique of separation of variables and applying the initial conditions, the following is obtained:

$E(t) \geq E_0 e^{-(\tau\lambda+k+\mu)t}$. Since $E_0 > 0$ and $e^{-(\tau\lambda+k+\mu)t}$ is also positive, then we can conclude that: $E(t) \geq E_0 e^{-(\tau\lambda+k+\mu)t} > 0$.

4. Let us consider the fourth differential equation

$\dot{I} = (\tau\lambda + k)E - (d + \delta_1 + \sigma + \mu)I$. This implies $dE/dt = (\tau\lambda + k)E - (d + \delta_1 + \sigma + \mu)I$.

After solving using the technique of separation of variables and applying the initial conditions, the following is obtained:

$I(t) \geq I_0 e^{-(d+\delta\_1+\sigma+\mu)t}$. Since $I_0 > 0$ and $e^{-(d+\delta\_1+\sigma+\mu)t}$ is also positive, then we can conclude that $I(t) \geq I_0 e^{-(d+\delta\_1+\sigma+\mu)t} > 0$.

5. Let us consider the fifth differential equation

$\dot{R} = (\delta_1 + \sigma)I + \delta_2 V - (\gamma\lambda + \mu)R$. $dR/dt + (\gamma\lambda + \mu)R = (\delta_1 + \sigma)I + \delta_2 V$.

After solving using the technique of separation of variables and applying the initial conditions, the following is obtained:

$R(t) \geq R_0 e^{-(\gamma\lambda+\mu)t}$. Since $R_0 > 0$ and $e^{-(\gamma\lambda+\mu)t}$ is also positive, then we can conclude that $R(t) \geq R_0 e^{-(\gamma\lambda+\mu)t} > 0$.

This completes the proof of the theorem. Therefore, the solution of the model is positive.

Theorem 2 (Boundedness)

To show the boundedness of the solution, we have to show a lower bound and upper bound. But, initially, $N(0) = N_0 > 0$, $S(0) = S_0 > 0$, $V(0) = V_0 > 0$, $E(0) = E_0 > 0$, $I(0) = I_0 > 0$, $R(0) = R_0 > 0$.

These initial conditions are considered as lower bounds. Now, we are going to show the upper bound. By taking the relation

$N(t) = S(t) + V(t) + E(t) + I(t) + R(t)$

and differentiating both sides of the equation with respect to time, we get: $dN/dt = dS/dt + dV/dt + dE/dt + dI/dt + dR/dt$

After simplification, we get:

$\Rightarrow dN/dt = b - \mu N - dI$

Then, by using integration by parts and applying initial condition $N(0) = N_0$ at $t = 0$, In the absence of mortality due to Hepatitis B virus, that is at d=0,and after simplification we get:

$\Rightarrow N \leq b/\mu\ (b-\mu N_0)\ e^{-\mu t}) / \mu$

As $t \to \infty$, the population size $N \to b/\mu$ since $(b-\mu N_0)e^{-\mu t}/\mu \to 0$, as $t \to \infty$.

This implies that $0 \leq N \leq b/\mu$.Thus, feasible solution set of the system equation of the model enters and remains in the region.

$\Omega = \{(S,V,E,I,R) \in R_+^5 : N \leq b/\mu\}$

Therefore, the basic model is well posed epidemiologically and mathematically. Hence, it is sufficient to study the dynamics of the basic model in Ω.

Disease-free Equilibrium Point (DFEP)

We calculate disease-free equilibrium point (DFEP) at $E^I=0, I^I=0$ by equating each system of differential equation to zero.

From (1) we have $\dot{S} = b-(\theta+\mu+\lambda)S = 0$. Since $\lambda = \frac{\beta c I}{N}$. At $I=0$, we get $\lambda = 0$.

This gives us: $S^1 = \frac{b}{\theta+\mu}$ (6)

From (2) we have: $\dot{V} = \theta S - (\delta_2+\mu)V = 0$. This gives us $V^1 = \frac{b\theta}{(\theta+\mu)(\delta_2+\mu)}$ (7)

From (5) we have: $\dot{R} = (\delta_1+\sigma)I + \delta_2 V - (\gamma\lambda+\mu)R = 0.$

This gives us: $R^1 = \frac{b\theta\,\delta_2}{\mu(\theta+\mu)(\delta_2+\mu)}.$ (8)

Then, DFEP is given by: $D^1 = (S^1, V^1, E^1, I^1, R^1)$

$$= \left(\frac{b}{\theta+\mu}, \frac{b\theta}{(\theta+\mu)(\delta_2+\mu)}, 0, 0, \frac{b\theta\,\delta_2}{\mu(\theta+\mu)(\delta_2+\mu)}\right).$$

Effective Reproduction Number(R_{Eff})

We find the effective reproduction number by using the next generation matrix method such that the reproduction number is the dominant eigenvalue of the next generation matrix $G=FV^{-1}$ where F represents new infection and V represents transfer of infections from one compartment to another.

Now, to find the reproduction number R_{eff} by using the next generation method, we can rearrange the differential equations of the dynamical systems (1-5) as follows.

$$F = \begin{pmatrix} 0 & \left(\frac{\beta c S^0}{N} + \frac{\gamma\beta c R^0}{N}\right) \\ 0 & 0 \end{pmatrix}, V = \begin{pmatrix} (k+\mu) & -\frac{\gamma\beta c R^0}{N} \\ -k & -\frac{\tau\beta c}{N} + (d+\delta_1+\sigma+\mu) \end{pmatrix} \text{ where:}$$

$N = S^0 + V^0$ and $\frac{S^0}{N} = \frac{S^0}{S^0+V^0} = \frac{(\delta_2+\mu)}{(\delta_2+\mu+\theta)}.\frac{R^0}{N} = \frac{\theta\,\delta_2}{\mu(\delta_2+\mu+\theta)}.$

$$\text{Then, } V^{-1} = \begin{pmatrix} \frac{-\frac{\tau\beta c}{b(\delta_2+\mu+\theta)}+(d+\delta_1+\sigma+\mu)}{\frac{-\tau\beta c}{(\delta_2+\mu+\theta)}+b(d+\delta_1+\sigma+\mu)+\frac{\gamma\beta c k\mu\ (\delta_1+\theta+\mu)}{\theta\,\delta_2}} & \frac{-\gamma\beta c\mu\ (\delta_1+\theta+\mu)}{\theta\,\delta_2\left(\frac{-\tau\beta c}{(\delta_2+\mu+\theta)}+b(d+\delta_1+\sigma+\mu)+\frac{\gamma\beta c k\mu\ (\delta_1+\theta+\mu)}{\theta\,\delta_2}\right)} \\ \frac{k}{\frac{-\tau\beta c}{(\delta_2+\mu+\theta)}+b(d+\delta_1+\sigma+\mu)+\frac{\gamma\beta c k\mu\ (\delta_1+\theta+\mu)}{\theta\,\delta_2}} & \frac{k+\mu}{\frac{-\tau\beta c}{(\delta_2+\mu+\theta)}+b(d+\delta_1+\sigma+\mu)+\frac{\gamma\beta c k\mu\ (\delta_1+\theta+\mu)}{\theta\,\delta_2}} \end{pmatrix}$$

$$\text{This implies, } FV^{-1} = \begin{pmatrix} \frac{\frac{\beta c k\ (\delta_2+\mu)}{(\delta_2+\mu+\theta)}}{\frac{-\tau\beta c}{(\delta_2+\mu+\theta)}+b(d+\delta_1+\sigma+\mu)+\frac{\gamma\beta c k\mu\ (\delta_1+\theta+\mu)}{\theta\,\delta_2}} & \frac{b\frac{\beta c\ (\delta_2+\mu)}{(\delta_2+\mu+\theta)}}{\frac{-\tau\beta c}{(\delta_2+\mu+\theta)}+b(d+\delta_1+\sigma+\mu)+\frac{\gamma\beta c k\mu\ (\delta_1+\theta+\mu)}{\theta\,\delta_2}} \\ 0 & 0 \end{pmatrix}$$

The characteristic equation of the Jacobian matrix is given by:

$$\begin{vmatrix} \frac{\frac{\beta c k\ (\delta_2+\mu)}{(\delta_2+\mu+\theta)}}{\frac{-\tau\beta c}{(\delta_2+\mu+\theta)}+b(d+\delta_1+\sigma+\mu)+\frac{\gamma\beta c k\mu\ (\delta_1+\theta+\mu)}{\theta\,\delta_2}} & \frac{b\frac{\beta c\ (\delta_2+\mu)}{(\delta_2+\mu+\theta)}}{\frac{-\tau\beta c}{(\delta_2+\mu+\theta)}+b(d+\delta_1+\sigma+\mu)+\frac{\gamma\beta c k\mu\ (\delta_1+\theta+\mu)}{\theta\,\delta_2}} \\ 0 & 0 \end{vmatrix}$$

$= 0$

The eigenvalues of the matrix are given by: $\{\lambda_1, \lambda_2\} = \left\{0, \frac{\frac{\beta c k\ (\delta_2+\mu)}{(\delta_2+\mu+\theta)}}{\frac{-\tau\beta c}{(\delta_2+\mu+\theta)}+b(d+\delta_1+\sigma+\mu)+\frac{\gamma\beta c k\mu\ (\delta_1+\theta+\mu)}{\theta\,\delta_2}}\right\}.$

Then, spectral radius of the characteristic equation is given by:

$\lambda = \frac{\frac{\beta c k\ (\delta_2+\mu)}{(\delta_2+\mu+\theta)}}{\frac{-\tau\beta c}{(\delta_2+\mu+\theta)}+b(d+\delta_1+\sigma+\mu)+\frac{\gamma\beta c k\mu\ (\delta_1+\theta+\mu)}{\theta\,\delta_2}}$ and simplified to:

$$\lambda = \frac{\beta ck\theta\ \delta_2(\delta_2+\mu)}{[-\tau\beta c\theta\ \delta_2+b\theta\delta_2(\delta_2+\mu+\theta)(d+\delta_1+\sigma+\mu)+\gamma\beta ck\mu\ (\delta_1+\theta+\mu)(\delta_2+\mu+\theta)]}.$$

Then the Effective reproduction number $\left(R_{Eff}\right)$ becomes:

$$R_{Eff} = \frac{\beta ck\theta\ \delta_2(\delta_2+\mu)}{[-\tau\beta c\theta\ \delta_2+b\theta\delta_2(\delta_2+\mu+\theta)(d+\delta_1+\sigma+\mu)+\gamma\beta ck\mu\ (\delta_1+\theta+\mu)(\delta_2+\mu+\theta)]}.$$

Endemic Equilibrium Point(EEP)

It is obtained by equating differential equation (1)-(5) to zero and solving it.

From (1) we have: $\dot{S} = \quad b-(\theta+\mu+\lambda)S = 0$. This gives us:

$$S_1 = \frac{b}{\theta+\mu+\lambda}. \tag{9}$$

From (2), we have: $\dot{V} = \theta S-(\delta_2+\mu)V = 0$. This gives us:

$$V_1 = \frac{\theta S}{\delta_2+\mu} = \frac{\Lambda\theta}{(\delta_2+\mu)(\theta+\mu+\lambda)} \tag{10}$$

From (3) we have: $\dot{E} = \lambda S+\gamma\lambda R-(\delta_1\lambda+k+\mu)E = 0$. This gives us:

$$E_1 = \frac{b\lambda}{(\mu+\lambda+k)(\theta+\mu+\lambda)} + \frac{\gamma\lambda\,[(\rho+\mu)(\delta_1\lambda+k)(\delta_2+\mu)+\delta_2 b\theta\,(\mu+\delta_1+\sigma+d)]}{(\mu+\lambda+k)[(\theta+\mu+\lambda)(\delta_2+\mu)(\mu+\delta_1+\sigma+d)-\delta_2\lambda(d+\mu)(\mu+\lambda+k)]} \tag{11}$$

From (4), we have: $\dot{I} = (\delta_1\lambda+k)E-(\rho+\varphi+\mu)I = 0$. This gives us:

$$I_1 = \frac{(\delta_1+k)}{(\mu+\varphi+\rho)}\left[\frac{b\lambda}{(\mu+\lambda+k)(\theta+\mu+\lambda)} + \frac{\gamma\lambda\,[(\rho+\mu)(\delta_1+k)(\delta_2+\mu)+\delta_2 b\theta\,(\mu+\delta_1+\sigma+d)]}{(\mu+\lambda+k)[(\theta+\mu+\lambda)(\delta_2+\mu)(\delta_2\lambda+\mu)(\mu+\delta_1+\sigma+d)-\delta_2\lambda(d+\mu)(\mu+\lambda+k)]}\right] \tag{12}$$

From (5), we have: $\dot{R} = (\delta_1+\sigma)I+\delta_2 V-(\gamma\lambda+\mu)R = 0$. This gives us:

$$R_1 = \frac{(\rho+\mu)(\delta_1+k)(\delta_2+\mu)+\delta_2 b\theta\,(\mu+\varphi+\rho)}{(\theta+\mu+\lambda)(\delta_2+\mu)(\delta_2\lambda+\mu)(\mu+\varphi+\rho)-\delta_2\lambda(\rho+\mu)(\mu+\lambda+k)}. \tag{13}$$

Then, Endemic Equilibrium Point (EEP) is given by: $D^* = (S_1, V_1, E_1, I_1, R_1)$ where:

$$S_1 = \frac{b}{\theta+\mu+\lambda}, V_1 = \frac{\theta S}{\delta_2+\mu} = \frac{\Lambda\theta}{(\delta_2+\mu)(\theta+\mu+\lambda)},$$

$$E_1 = \frac{b\lambda}{(\mu+\lambda+k)(\theta+\mu+\lambda)} + \frac{\gamma\lambda[(d+\mu)(\delta_1+k)(\delta_2+\mu)+\delta_2 b\theta(\mu+\delta_1+\sigma+d)]}{(\mu+\lambda+k)[(\theta+\mu+\lambda)(\delta_2+\mu)(\delta_2\lambda+\mu)(\mu+\delta_1+\sigma+d)-\delta_2\lambda(\rho+\mu)(\mu+\lambda+k)]},$$

$$I_1 = \frac{(\delta_1 + k)}{(\mu + \delta_1 + \sigma + d)}\left[\frac{b\lambda}{(\mu + \lambda + k)(\theta + \mu + \lambda)} + \frac{\gamma\lambda[(\rho + \mu)(\delta_1 + k)(\delta_2 + \mu) + \delta_2 b\theta(\mu + \delta_1 + \sigma + d)]}{(\mu + \lambda + k)[(\theta + \mu + \lambda)(\delta_2 + \mu)(\delta_2\lambda + \mu)(\mu + \delta_1 + \sigma + d) - \delta_2\lambda(d + \mu)(\mu + \lambda + k)]}\right]$$

$$R_1 = \frac{(d + \mu)(\delta_1 + k)(\delta_2 + \mu) + \delta_2 b\theta(\mu + \delta_1 + \sigma + d)}{(\theta + \mu + \lambda)(\delta_2 + \mu)(\delta_2\lambda + \mu)(\mu + \delta_1 + \sigma + d) - \delta_2\lambda(d + \mu)(\mu + \lambda + k)}$$

Local Stability Analysis of Disease-free Equilibrium Point (DFEP)

$$J(D^1) = \begin{pmatrix} -(\theta + \mu) & 0 & 0 & 0 & 0 \\ \theta & -(\delta_2 + \mu) & 0 & 0 & 0 \\ 0 & 0 & -(\mu + k) & \left(\frac{\beta c S_1}{N} + \frac{\gamma\beta c R_1}{N}\right) & 0 \\ 0 & 0 & k & -(\mu + \delta_1 + \sigma + d) & 0 \\ 0 & \delta_2 & 0 & \left(\delta_1 + k - \frac{\gamma\beta c R_1}{N}\right) & -\mu \end{pmatrix}$$

Let $a = \theta + \mu, b = \delta_2 + \mu, c = \mu + k, d = \left(\frac{\beta c S_1}{N} + \frac{\gamma\beta c R_1}{N}\right), e = \mu + \delta_1 + \sigma + d, f = \left(\delta_1 + k - \frac{\gamma\beta c R_1}{N}\right)$

Then, the characteristic equation of the Jacobian matrix is given by:

$$\begin{vmatrix} -(\theta + \mu) & 0 & 0 & 0 & 0 \\ \theta & -(\delta_2 + \mu) & 0 & 0 & 0 \\ 0 & 0 & -(\mu + k) & \left(\frac{\beta c S_1}{N} + \frac{\gamma\beta c R_1}{N}\right) & 0 \\ 0 & 0 & k & -(\mu + \delta_1 + \sigma + d) & 0 \\ 0 & \delta_2 & 0 & \left(\delta_1 + k - \frac{\gamma\beta c R_1}{N}\right) & -\mu \end{vmatrix} = 0$$

Then, the determinant gives us:

$\left(\frac{1}{2}(-c - e - \sqrt{c^2 - 2ce + e^2 + 4dk} - 2\lambda)\right)\left(\frac{1}{2}(-c - e + \sqrt{c^2 - 2ce + e^2 + 4dk} - 2\lambda)\right)(-a - \lambda)(-b - \lambda)(-\lambda - \mu) = 0$. From this we have:

$\lambda_1 = -a \; or \; \lambda_2 = -b, \lambda_3 = -\mu, \lambda_4 = \frac{1}{2}\left(-c - e - \sqrt{c^2 - 2ce + e^2 + 4dk}\right) \; or \; \lambda_5 = \frac{1}{2}\left(-c - e + \sqrt{c^2 - 2ce + e^2 + 4dk}\right)$.

As it is shown above, the eigenvalues $\lambda_1, \lambda_2$and$\lambda_3$are negatives and λ_4 and λ_5 have negative real parts. Then, we can conclude that Disease free equilibrium point is locally asymptotically stable.

Local stability Analysis of Endemic Equilibrium Point (EEP)

$$J(E^*) = \begin{pmatrix} -(\theta+\mu+\lambda) & 0 & 0 & 0 & 0 \\ \theta & -(\delta_2+\mu) & 0 & 0 & 0 \\ \lambda & 0 & -(\tau\lambda+\mu+k) & \left(\frac{\beta c S_1}{N}+\frac{\gamma\beta c R_1}{N}\right) & \gamma\lambda \\ 0 & 0 & (\tau\lambda+k) & \frac{\tau\beta c E}{N}-(\mu+\delta_1+\sigma+d) & 0 \\ 0 & \delta_2 & 0 & \left(\delta_1+k-\frac{\gamma\beta c R_1}{N}\right) & -(\gamma\lambda+\mu) \end{pmatrix}$$

Let $A=\theta+\mu+\lambda, B=\delta_2+\mu, C=\tau\lambda+\mu+k, D=\left(\frac{\beta c S_1}{N}+\frac{\gamma\beta c R_1}{N}\right), H=\tau\lambda+k, I=\frac{\tau\beta c E}{N}-(\mu+\delta_1+\sigma+d), J=\left(\delta_1+k-\frac{\gamma\beta c R_1}{N}\right), K=\gamma\lambda+\mu)$

Then, the characteristic equation of the Jacobian matrix is given by:

$$\begin{vmatrix} -(\theta+\mu+\lambda) & 0 & 0 & 0 & 0 \\ \theta & -(\delta_2+\mu) & 0 & 0 & 0 \\ \lambda & 0 & -(\tau\lambda+\mu+k) & \left(\frac{\beta c S_1}{N}+\frac{\gamma\beta c R_1}{N}\right) & \gamma\lambda \\ 0 & 0 & (\tau\lambda+k) & \frac{\tau\beta c E}{N}-(\mu+\delta_1+\sigma+d) & 0 \\ 0 & \delta_2 & 0 & \left(\delta_1+k-\frac{\gamma\beta c R_1}{N}\right) & -(\gamma\lambda+\mu) \end{vmatrix} = 0$$

Determinant of the characteristic equation gives us:

$(-A-\lambda)(-B-\lambda)(\lambda^3+(C+K+I+3)\lambda^2+(IC-DH+IK+CK+2I+2C+2K+3)\lambda+ \text{i}K+CK+\text{i}+C+K-GHJ+\text{i}CK-DHK)=0$.This implies $\lambda_1=-A \text{ or } \lambda_2=-B$ or $(\lambda^3+(C+K+I+3)\lambda^2+(IC-DH+IK+CK+2I+2C+2K+3)\lambda+\text{i}K+CK+\text{i}+ C+K-GHJ+\text{i}CK-DHK)=0$.

Let us check for $\lambda^3+(C+K+I+3)\lambda^2+(IC-DH+IK+CK+2I+2C+2K+3)\lambda+ (\text{i}K+CK+\text{i}+C+K-GHJ+\text{i}CK-DHK)=0$. Here $a_0\lambda^3+a_1\lambda^2+a_2\lambda+a_3=0$.

Then, $a_0=1, a_1=(C+K+I+3), a_2=(IC-DH+IK+CK+2I+2C+2K+3), a_3= (\text{i}K+CK+\text{i}+C+K-GHJ+\text{i}CK-DHK)$.

So, for $\lambda^3 + (C + K + I + 3)\lambda^2 + (IC - DH + IK + CK + 2I + 2C + 2K + 3)\lambda + \mathbb{i}K + CK + \mathbb{i} + C + K - GHJ + \mathbb{i}CK - DHK) = 0$,

$$\begin{array}{c|c} & a_0 a_2 \\ S^3 & a_1 a_3 \\ S^2 & \frac{a_1 a_2 - a_0 a_3}{a_1} \\ S^1 & \\ S^0 & a_3 \end{array}$$

$$i) a_0 = 1 > 0.$$

$$ii) a_3 > 0.$$

$iii)$ $\frac{a_1 a_2 - a_0 a_3}{a_1} > 0$ implies $a_1 a_2 - a_0 a_3 > 0$.Then,$a_1 a_2 - a_0 a_3 = (C + K + I + 3)(IC - DH + IK + CK + 2I + 2C + 2K + 3) - (\mathbb{i}K + CK + \mathbb{i} + C + K - GHJ + \mathbb{i}CK - DHK) > 0$ which is valid.

Therefore, we can conclude that the Endemic Equilibrium Point is locally asymptotically stable.

Global Stability of Disease-Free Equilibrium Point (DFEP)

Theorem 3:

The Disease-Free Equilibrium Point (DFEP)D^1 is given by:

$D^1 = (S^1, V^1, E^1, I^1, R^1) = \left(\frac{b}{\theta+\mu}, \frac{b\theta}{(\theta+\mu)(\delta_2+\mu)}, 0, 0, \frac{b\theta\,\delta_2}{\mu(\theta+\mu)(\delta_2+\mu)}\right)$ is globally asymptotically stable if $R_{Eff} < 1$.

Proof:

We construct a Lyapunov function by:$L = \alpha_1 E + \alpha_2 I$. This implies:

$$\dot{L} = \alpha_1 \dot{E} + \alpha_2 \dot{I}$$

$$\dot{L} = \alpha_1 E + \alpha_2 I = \alpha_1(\lambda S + \gamma\lambda R - (\tau\lambda + k + \mu)E) + \alpha_2((\tau\lambda + k)E - (d + \delta_1 + \sigma + \mu)I)$$

Collecting like terms and simplifying gives us:

$$\dot{L} = \alpha_1 \left(\frac{\beta c I}{N} S^1 + \gamma \frac{\beta c I}{N} R^1 - \mu\right) E - \alpha_2 (d + \delta_1 + \sigma + \mu) I$$

$$\dot{L} \leq \alpha_1(d+\delta_1+\sigma+\mu)\left(\left(\frac{\beta cI}{N}S^1+\gamma\frac{\beta cI}{N}R^1\right)-1\right) \text{ where } S^1=\frac{b}{\theta+\mu}, R^1=\frac{b\theta\,\delta_2}{\mu(\theta+\mu)(\delta_2+\mu)}.$$

$$\dot{L} \leq \alpha_1\alpha_2(d+\delta_1+\sigma+\mu)\left(R_{Eff}-1\right)$$

Then, we note that $\frac{dL}{dt} \leq 0$ if $R_{Eff} < 1$.Furthermore, $\frac{dL}{dt} = 0$ if and only if $E = I = 0$. Therefore, the largest compact invariant set in $(S, V, E, I, R) \in \Omega$: $\frac{dL}{dt} < 0$ where $R_{Eff} < 1$ is the singleton $\{E^1\}$. Lasalle's (1976) invariance principle then implies that D^1 is globally stable in Ω if $R_{Eff} < 1$ otherwise it is unstable.

Global Stability of Endemic Equilibrium Point (EEP)

Liao and Wang proposed a combination of the Lyapunov function method and Volterra–Lyapunov properties and proved the global asymptotic stability of the endemic equilibria. This method does not meet the challenges of the Lyapunov function method, including determining the appropriate Lyapunov function and coefficients [1].

In this work, we will present a modification of the method of Lyapunov functions combined with the theory of Volterra–Lyapunov stable matrices [1, 2].The fundamental difference between the two methods is that our modified method repeatedly uses Lemma 1, Lemma 2, and reduces the dimensions of the matrices, while in some parts of the original method this technique is not used. We will analyze the global stability of the endemic equilibrium points applying the approach in [7]. $L=\sum_{i=1}^{5} w_i\ (x_i - x_i^*)^2$ where w_i is properly selected positive constant, x_i is the population of i^{th} compartment and x_i^* is the equilibrium point. This approach has been found to be useful for more complex compartmental epidemic models [8].

Theorem 5:

The endemic equilibrium point $D^* = (S^*, V^*, E^*, I^*, R^*)$

of the dynamical system of HBV, model of (1 – 5) is globally asymptotically stable (GAS) if $R_{eff} > 1$.

Proof: - Let the Lyapunov function $R_+^5 \to R_+$ is defined by:

$L = w_1(S-S^*)^2 + w_2(V-V^*)^2 + w_3(E-E^*)^2 + w_4(I-I^*)^2 + w_1(R-R^*)^2$where w_1, w_2, w_3, w_4,and $w_5$are positive constants. Calculating the time derivative of L along the trajectories of equations (1-5). We obtain:

$$\frac{dL}{dt} = 2w_1(S-S^*)\dot{S} + 2w_2(V-V^*)\dot{V} + 2w_3(E-E^*)\dot{E} + 2w_4(I-I^*)\dot{A} + 2w_5(R-R^*)\dot{R}$$

$$\begin{aligned}\frac{dL}{dt} = {} & 2w_1(S-S^*)(b-(\theta+\mu+\lambda)S) + 2w_2(V-V^*)(\theta S-(\delta_2+\mu)V) \\ & + 2w_3(E-E^*)(\lambda S+\gamma\lambda R-(\tau\lambda+k+\mu)E) \\ & + 2w_4(I-I^*)((\tau\lambda+k)E-(d+\delta_1+\sigma+\mu)I) \\ & + 2w_5(R-R^*)\left((\delta_1+\sigma)I+\delta_2 V-(\gamma\lambda+\mu)R\right)\end{aligned}$$

After some calculation and simplifications, we get:

$\dot{L} = Y(WA + A^T W)Y^T$ where $Y = [S - S^*, V - V^*, E - E^*, I - I^*, R - R^*]$

$W = diag(w_1, w_2, w_3, w_4, w_5)$ and

$$A = \begin{bmatrix} -(\theta+\mu) & 0 & 0 & 0 & 0 \\ \theta & -(\delta_2+\mu) & 0 & 0 & 0 \\ 0 & 0 & -(\mu+k) & \left(\frac{\beta c S_1}{N} + \frac{\gamma \beta c R_1}{N}\right) & 0 \\ 0 & 0 & k & -(\mu+\delta_1+\sigma+d) & 0 \\ 0 & \delta_2 & 0 & \left(\delta_1 + k - \frac{\gamma \beta c R_1}{N}\right) & -\mu \end{bmatrix} \quad (9)$$

To establish the global stability of the endemic equilibrium E^*, we investigate that the matrix A defined in (9) is Volterra-Lyapunov stable. Below, we briefly review the following pre-requisites. Here, we recall the basic definitions related to Volterra-Lyapunov stable matrices. Suppose $A_{n\times n}$ is real matrix.

(D_1) All the eigenvalues of A have negative (positive) real parts if and only if there exists a matrix $H > 0$ (that means H is symmetric positive definite) such that $HA + A^T H^T < 0 (> 0)$.

(D_2) The non-singular matrix $A_{n\times n}$ is diagonal matrix $M_{n\times n}$ such that $MA + A^T M^T > 0$.

L_1: The $D = \begin{bmatrix} d_{11} & d_{12} \\ d_{21} & d_{22} \end{bmatrix}$ is Volterra-Lyapunov stable if and only if

$d_{11} < 0, d_{22} < 0 \Rightarrow \det(D) = d_{11}d_{22} - d_{12}d_{21} > 0.$

L_2: Suppose the non-singular $D_{n\times n} = [d_{ij}], (n \geq 2)$,

$M_{n\times n} = diag(m_1, \ldots, m_n)$ is a positive diagonal matrix and $H = D^{-1}$ such that:

1. $d_{nn} > 0$
2. $\widetilde{M}\widetilde{D} + (\widetilde{M}\widetilde{D})^T > 0$
3. $\widetilde{M}\widetilde{H} + (\widetilde{M}\widetilde{H})^T > 0$
4. it is possible to choose $m_n > 0$ such that $\widetilde{M}\widetilde{D} + (\widetilde{M}\widetilde{D})^T > 0$

Note that $\widetilde{D}$ denote the $(n-1) \times (n-1)$ matrix obtained from D by deleting its last row and last column.

Theorem 6:

The matrix A defined in equation (9) is Volterra-Lyapunov stable.

Proof:

We have:

$$A = \begin{bmatrix} -(\theta+\mu) & 0 & 0 & 0 & 0 \\ \theta & -(\delta_2+\mu) & 0 & 0 & 0 \\ 0 & 0 & -(\mu+k) & \left(\frac{\beta c S_1}{N} + \frac{\gamma\beta c R_1}{N}\right) & 0 \\ 0 & 0 & k & -(\mu+\delta_1+\sigma+d) & 0 \\ 0 & \delta_2 & 0 & \left(\delta_1 + k - \frac{\gamma\beta c R_1}{N}\right) & -\mu \end{bmatrix}$$

Then,

$$-A = \begin{bmatrix} (\theta+\mu) & 0 & 0 & 0 & 0 \\ \theta & (\delta_2+\mu) & 0 & 0 & 0 \\ 0 & 0 & (\mu+k) & -\left(\frac{\beta c S_1}{N} + \frac{\gamma\beta c R_1}{N}\right) & 0 \\ 0 & 0 & -k & (\mu+\delta_1+\sigma+d) & 0 \\ 0 & -\delta_2 & 0 & -\left(\delta_1 + k - \frac{\gamma\beta c R_1}{N}\right) & \mu \end{bmatrix}$$

Clearly, $-A_{55} = -\big(-(\theta+\mu)\big) = (\theta+\mu) > 0$. Let us consider $D = -\tilde{A}$,denote the 4×4 matrix obtained from $-A$ by deleting its last row and last column. From equation (11), we obtain:

$$D = -\tilde{A} = \begin{bmatrix} (\theta+\mu) & 0 & 0 & 0 \\ \theta & (\delta_2+\mu) & 0 & 0 \\ 0 & 0 & (\mu+k) & -(\frac{\beta c S_1}{N} + \frac{\gamma\beta c R_1}{N}) \\ 0 & 0 & -k & (\mu+\delta_1+\sigma+d) \end{bmatrix} \quad (10)$$

Based on L_2, we state and prove the following results.

The first Lemma proves that $D = -\tilde{A}$ is diagonal stable and in the next lemma, we show the $H = -\widetilde{A^{-1}}$ is diagonal stable. Therefore, all the conditions of (L_2) are satisfied. Hence, the matrix A is a Volterra-Lyapunov stable.

Lemma 1:

The matrix D defined in Equation (10) is diagonal stable.

Proof:

Let us discuss the diagonal stability of D. It is guaranteed by the following steps.

Step 1: $D_{44} > 0$.

Step 2: By using L_2, we shall prove that the matrix $\widetilde{D}$ is diagonal stable. From (10), we obtain

$$\widetilde{D} = \begin{bmatrix} (\theta+\mu) & 0 & 0 \\ \theta & (\delta_2+\mu) & 0 \\ 0 & 0 & (\mu+k) \end{bmatrix}$$

Obviously, $\widetilde{D}_{11} > 0, \widetilde{D}_{22} > 0$,nd$\widetilde{D}_{33} > 0$. It remains to show that $det(\widetilde{D}) > 0$.

$\Rightarrow det(\widetilde{D}) = (k+\mu)(\theta+\mu)(\mu+\delta_2) > 0$. Therefore, $\widetilde{D}$ is diagonally stable.

Step 3: Now we must show that $\widetilde{D^{-1}}$ is diagonally stable.

$$\widetilde{D^{-1}} = \begin{bmatrix} \frac{1}{\theta+\mu} & 0 & 0 \\ \frac{-k\theta-\theta\mu}{(k+\mu)(\theta+\mu)(\mu+\delta_2)} & \frac{1}{\mu+\delta_2} & 0 \\ 0 & 0 & \frac{1}{k+\mu} \end{bmatrix}$$

It is easy to see $\widetilde{D^{-1}}_{11} = \frac{1}{\theta+\mu} > 0, \widetilde{D^{-1}}_{22} = \frac{1}{\mu+\delta_2} > 0, \widetilde{D^{-1}}_{33} = \frac{1}{k+\mu} > 0$. Therefore, $\widetilde{D^{-1}}$ is diagonal stable.

Lemma 2: The matrix $H = \widetilde{-A^{-1}}$ is diagonal stable.

Proof:

We obtain the $\widetilde{-A^{-1}}$ as following.

$$H = \widetilde{-A^{-1}} = \frac{1}{\det(-A)} Adj(-A)$$

We have :

$$A = \begin{bmatrix} -(\theta+\mu) & 0 & 0 & 0 & 0 \\ \theta & -(\delta_2+\mu) & 0 & 0 & 0 \\ 0 & 0 & -(\mu+k) & \left(\frac{\beta c S_1}{N} + \frac{\gamma\beta c R_1}{N}\right) & 0 \\ 0 & 0 & k & -(\mu+\delta_1+\sigma+d) & 0 \\ 0 & \delta_2 & 0 & \left(\delta_1 + k - \frac{\gamma\beta c R_1}{N}\right) & -\mu \end{bmatrix}$$

Let $B = -A$ then,

where

$$B = \begin{bmatrix} (\theta+\mu) & 0 & 0 & 0 & 0 \\ \theta & (\delta_2+\mu) & 0 & 0 & 0 \\ 0 & 0 & (\mu+k) & -\left(\frac{\beta c S_1}{N} + \frac{\gamma\beta c R_1}{N}\right) & 0 \\ 0 & 0 & -k & (\mu+\delta_1+\sigma+d) & 0 \\ 0 & -\delta_2 & 0 & -\left(\delta_1 + k - \frac{\gamma\beta c R_1}{N}\right) & \mu \end{bmatrix}$$

$$-A^{-1} = B^{-1} = \begin{bmatrix} c_{11} & 0 & 0 & 0 & 0 \\ c_{21} & c_{22} & 0 & 0 & 0 \\ 0 & 0 & c_{33} & c_{34} & 0 \\ 0 & 0 & c_{43} & c_{44} & 0 \\ c_{51} & c_{52} & c_{53} & c_{54} & c_{55} \end{bmatrix}$$

Let $c_{11} = \frac{1}{\theta+\mu}, c_{21} = \frac{-dk\theta\mu - d\theta\mu^2 - k\theta\mu^2 - \theta\mu^3 - k\theta\mu\sigma - \theta\mu^2\sigma + \frac{ck\beta\gamma\theta\mu}{N} R_1 + \frac{ck\beta\theta\mu}{N} S_1 - k\theta\mu\delta_1 - \theta\mu^2\delta_1}{\mu(\theta+\mu)\left(dk + d\mu + k\mu + \mu^2 + k\sigma + \mu\sigma - \frac{ck\beta\gamma}{N} R_1 - \frac{ck\beta}{N} S_1 + k\delta_1 + \mu\delta_1\right)(\mu+\delta_2)}$,

$$c_{22} = \frac{1}{\mu+\delta_2}, c_{33} = \frac{d+\mu+\sigma+\delta_1}{dk + d\mu + k\mu + \mu^2 + k\sigma + \mu\sigma - \frac{ck\beta\gamma}{N} R_1 - \frac{ck\beta}{N} S_1 + k\delta_1 + \mu\delta_1},$$

$$c_{34} = -\frac{-\frac{c\beta\gamma}{N} R_1 - \frac{c\beta}{N} S_1}{dk + d\mu + k\mu + \mu^2 + k\sigma + \mu\sigma - \frac{ck\beta\gamma}{N} R_1 - \frac{ck\beta}{N} S_1 + k\delta_1 + \mu\delta_1},$$

$$c_{43} = \frac{k}{dk + d\mu + k\mu + \mu^2 + k\sigma + \mu\sigma - \frac{ck\beta\gamma R_1}{N} - \frac{ck\beta S_1}{N} + k\delta_1 + \mu\delta_1},$$

$$c_{44} = \frac{k+\mu}{dk + d\mu + k\mu + \mu^2 + k\sigma + \mu\sigma - \frac{ck\beta\gamma R_1}{N} - \frac{ck\beta S_1}{N} + k\delta_1 + \mu\delta_1}, c_{51}$$

$$= -\frac{\theta\delta_2}{\mu(\theta+\mu)(\mu+\delta_2)},$$

$$c_{52} = \frac{\delta_2}{\mu(\mu+\delta_2)}, c_{53} = -\frac{k\left(-k + \frac{c\beta\gamma R_1}{N} - \delta_1\right)}{\mu\left(dk + d\mu + k\mu + \mu^2 + k\sigma + \mu\sigma - \frac{ck\beta\gamma R_1}{N} - \frac{ck\beta S_1}{N} + k\delta_1 + \mu\delta_1\right)},$$

$$c_{54} = -\frac{(k+\mu)\left(-k + \frac{c\beta\gamma R_1}{N} - \delta_1\right)}{\mu\left(dk + d\mu + k\mu + \mu^2 + k\sigma + \mu\sigma - \frac{ck\beta\gamma R_1}{N} - \frac{ck\beta S_1}{N} + k\delta_1 + \mu\delta_1\right)}, c_{55} = \frac{1}{\mu}$$

then,

$$H = \widetilde{(-A^{-1})} = \begin{bmatrix} c_{11} & 0 & 0 & 0 \\ c_{21} & c_{22} & 0 & 0 \\ 0 & 0 & c_{33} & c_{34} \\ 0 & 0 & c_{43} & c_{44} \end{bmatrix}$$

It is obvious that:

$$H_{44} = c_{44} = \frac{k+\mu}{dk + d\mu + k\mu + \mu^2 + k\sigma + \mu\sigma - \frac{ck\beta\gamma R_1}{N} - \frac{ck\beta S_1}{N} + k\delta_1 + \mu\delta_1} > 0.$$

Below, we show that $\widetilde{H}$and$\widetilde{H^{-1}}$ are diagonally stable.

$$\widetilde{H} = \frac{1}{\det(-A)}\begin{bmatrix} c_{11} & 0 & 0 \\ c_{21} & c_{22} & 0 \\ 0 & 0 & c_{33} \end{bmatrix}$$

$$= \frac{N}{\mu(\theta+\mu)(k(-c\beta\gamma R_1 - c\beta S_1) + N(k+\mu)(d+\mu+\sigma+\delta_1))(\mu+\delta_2)}\begin{bmatrix} c_{11} & 0 & 0 \\ c_{21} & c_{22} & 0 \\ 0 & 0 & c_{33} \end{bmatrix}$$

$\widetilde{H} = \begin{bmatrix} e_{11} & 0 & 0 \\ d_{21} & e_{22} & 0 \\ 0 & 0 & e_{33} \end{bmatrix}$ where:

$$d_{11} = \frac{c_{11}N}{\mu(\theta+\mu)\big(k(-c\beta\gamma R_1 - c\beta S_1) + N(k+\mu)(d+\mu+\sigma+\delta_1)\big)(\mu+\delta_2)},$$

$$d_{21} = \frac{c_{21}N}{\mu(\theta+\mu)(k(-c\beta\gamma R_1 - c\beta S_1) + N(k+\mu)(d+\mu+\sigma+\delta_1))(\mu+\delta_2)},$$

$$d_{22} = \frac{c_{22}N}{\mu(\theta+\mu)\big(k(-c\beta\gamma R_1 - c\beta S_1) + N(k+\mu)(d+\mu+\sigma+\delta_1)\big)(\mu+\delta_2)},$$

$$d_{33} = \frac{c_{33}N}{\mu(\theta+\mu)(k(-c\beta\gamma R_1 - c\beta S_1) + N(k+\mu)(d+\mu+\sigma+\delta_1))(\mu+\delta_2)},$$

First, we show that $\det(-A) > 0$.

$$\det(-A) = \frac{N}{\mu(\theta+\mu)(k(-c\beta\gamma R_1 - c\beta S_1) + N(k+\mu)(d+\mu+\sigma+\delta_1))(\mu+\delta_2)} > 0.$$

Next, we check for $\det(\widetilde{H}) = e_{11}e_{22}e_{33} > 0$ which is valid.

It remains to show that $\widetilde{H^{-1}}$ is diagonal stable.

Define

$$\widetilde{H^{-1}} = \frac{1}{\det(H)}\begin{bmatrix} e_{11} & 0 & 0 \\ d_{21} & e_{22} & 0 \\ 0 & 0 & e_{33} \end{bmatrix} = \frac{1}{e_{11}e_{22}e_{33}}\begin{bmatrix} e_{11} & 0 & 0 \\ d_{21} & e_{22} & 0 \\ 0 & 0 & e_{33} \end{bmatrix} = \begin{bmatrix} \frac{1}{e_{22}e_{33}} & 0 & 0 \\ \frac{e_{21}}{e_{11}e_{22}e_{33}} & \frac{1}{e_{11}e_{33}} & 0 \\ 0 & 0 & \frac{1}{e_{11}e_{22}} \end{bmatrix}$$

$$= \begin{bmatrix} f_{11} & 0 & 0 \\ f_{21} & f_{22} & 0 \\ 0 & 0 & f_{33} \end{bmatrix} \quad \text{where } f_{11} = \frac{1}{e_{22}e_{33}}, f_{21} = \frac{e_{21}}{e_{11}e_{22}e_{33}}, f_{22} = \frac{1}{e_{11}e_{33}}, f_{33} = \frac{1}{e_{11}e_{22}}.$$

It is easy to show that $\det(\widetilde{H^{-1}}) = \frac{1}{f_{11}f_{22}f_{33}} > 0$.

Therefore, $\widetilde{H^{-1}}$ is a diagonal stable.

Summarizing the above discussions, we have the following conclusions for the globally asymptotically stability of the endemic equilibrium.

Theorem 7: When $R_{Eff} > 1$, the endemic equilibrium $E^*(S^*, V^*, E^*, I, R^*)$of Model (1-5) is globally asymptotically stable, in Ω.

Proof: Lemmas 1 and 2 with the aid of Theorem 1, guarantee that the endemic equilibrium of the model System (1-5) is globally asymptotically stable.

Numerical Simulation

Sensitivity Analysis

Definition: The normalized forward sensitivity index of R_{eff} that depends differentiable on a parameter P is defined by:

$$SI(P) = (\partial R_{eff}) / \partial P \times P/R_{eff}$$

Therefore, we calculated Sensitivity Index in terms of each parameter by using the parametric values from Table 2 below as follows.

Table 1:Parameters used in numerical simulation

Parameter	Description	Values Range	Reference
c	Contact rate	0.2-0.46	[2]
γ	re-infection rate	0.32	[31]
φ	Level of infectiousness of chronically infected population	0-1	[2]
θ	Vaccination rate	0.1-0.9	[9]
μ	Death rate	0.0121-0.05	[30]
b	Recruitment rate	0.11	[31]
k	Transfer rate from E to I	3 per year	[31]
σ	Treatment rate	0-0.045	[7]
δ_1	Natural recovery rate of Acutely infected population	0.05–0.9	[31]
δ_2	Rate of moving from Acute to recovery	0.04	[2]
φ	Recovery rate	0.32	[9]

The resulting sensitivity indices of R_{eff} to the seven different parameters in the model are shown in the following table in the order from the most sensitive to least.

Table 2: The sensitivity index of the parameters

Order		Sensitivity Index
1	σ	-1.830187
2	θ	-1.1216
3	γ	1.1
4	c	1
5	β	0.7654
6	k	0.6887
7	δ_1	-0.64427

The resulting sensitivity indices of R_{Eff} to the thirteen different parameters in the model are shown in the above table in the order from the most sensitive to least. From the sensitivity index of the model, we consider that the most sensitive parameter is σ , which is rate at which the infectious individuals at the chronic stage are isolated for treatment. The least sensitive parameter is δ_1,which is natural recovery rate of acutely infected population.

Stability of Disease-free equilibrium point of SVEIR model for effective reproduction number less than a unity

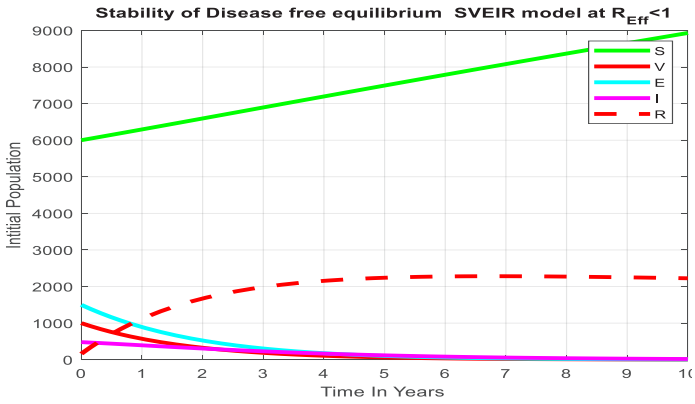

Figure 2: Graph of stability of SVEIR model for R_{Eff}<1.

As shown on Figure 2, above, at effective reproduction number less than one, susceptible population and recovered population increase whereas the remaining compartment (infectious class) decreases. This confirms that when average number of infected population that infect susceptible population in his/her lifetime becomes less than one, then the number of infected populations decreases and the diseases dies out.

Stability of infectious class of SVEIR model for R_{Eff} less than a unity

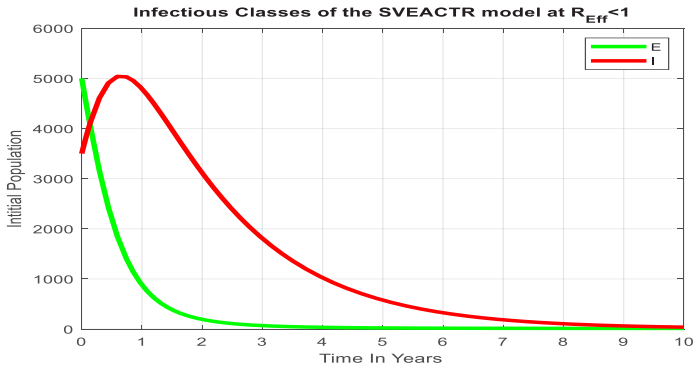

Figure 3: Graph of infectious class of SVEIR model for R_{Eff}<1.

From Figure 3,we can understand that at effective reproduction number less than a unity, the infectious class converges to zero. By keeping R_{Eff} less than one, the population can get rid of the HBV disease and enable the disease dies out.

Stability of SVEIR model for effective reproduction number greater than a unity

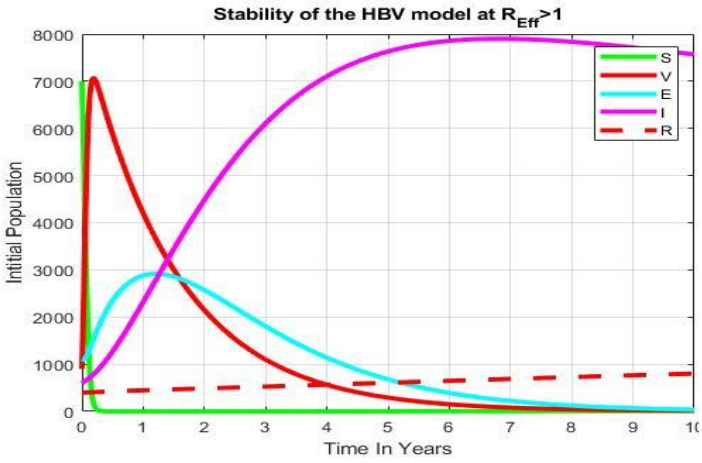

Figure 4: Stability of SVEIR model at R_{Eff}>1.

As shown on Figure 4, above, at effective reproduction number greater than a unity, the exposed population increases exponentially. This shows that as the average number of susceptible populations infected by infectious population becomes greater than one, then infected class increases in the reverse the number of susceptible populations decreases exponentially.

The role of Vaccination and treatment rate on reproduction number

Here, we will discuss the relation between intervention strategy parameters and the basic reproduction number.

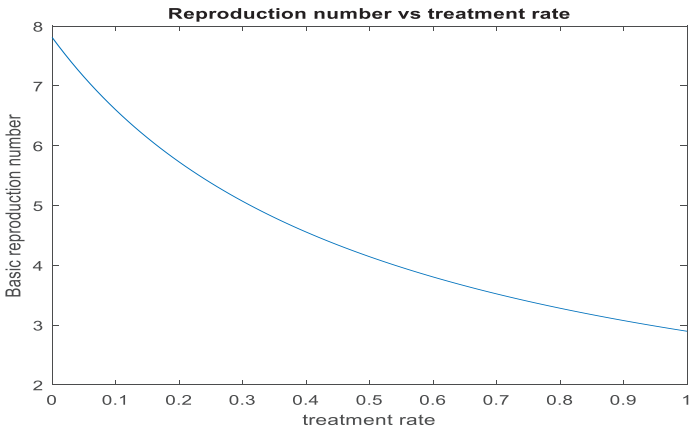

Figure 5: Reproduction number vs treatment rate

As it is shown on Figure 5, as we increase the rate of treatment of infected population, then reproduction number of HBV decreases. This shows treatment is one of the strategies that helps us to control spread and transmission of HBV.

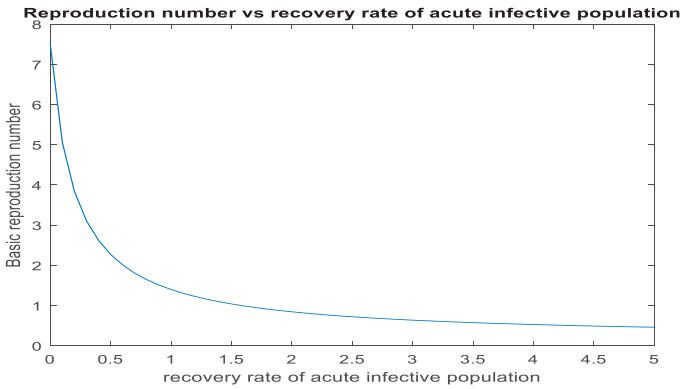

Figure 6: Reproduction number vs recovery rate of acute infective population

On Figure 6, it is shown that as natural recovery rate of acute infective population increases, reproduction number of HBV decreases. Then, by immunizing acutely infected population, it is possible to decrease transmission of HBV in the society.

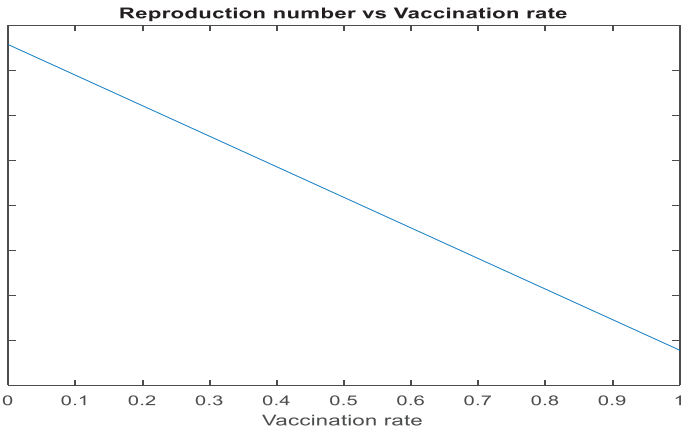

Figure 7: Reproduction number vs Vaccination rate

From Figure 7, we can understand that as we increase vaccination rate of the population, reproduction number of HBV decrease. This shows that vaccination is one of the best strategies to decrease transmission of HBV in the society. To do so, we should vaccinate large proportion of the society to get rid of HBV transmission.

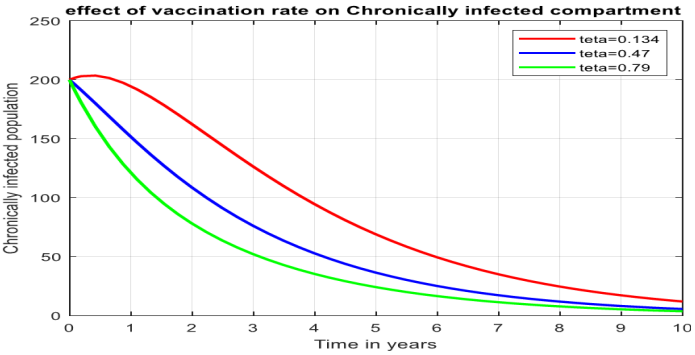

Figure 8: Effect of vaccination rate on infective population

In Figure 8, it is shown that as we increase the vaccination rate, the number of infective populations decreases. So, by subsequently vaccinating the population, it is possible to decrease the number of infective populations in the society.

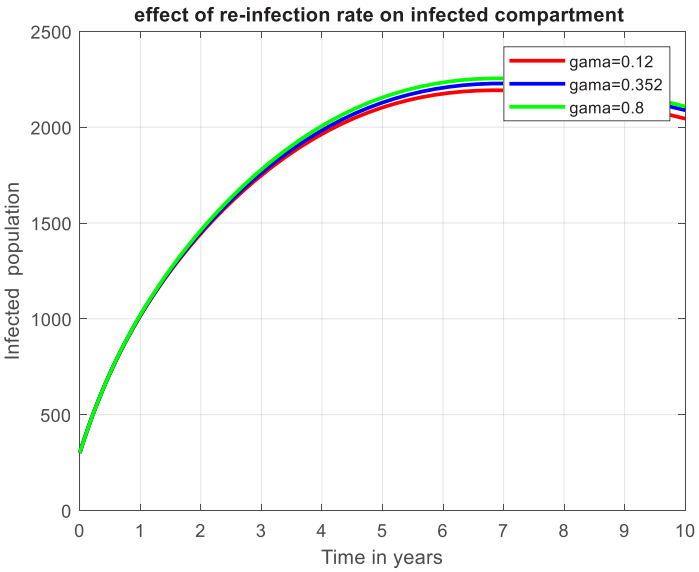

Figure 9: Effect of re-infection rate in infected population

As shown in Figure 9, as we increase re-infection rate, the number of infective populations also increases. From this we can understand that re-infection plays a great role in increasing number of infective populations in the society.

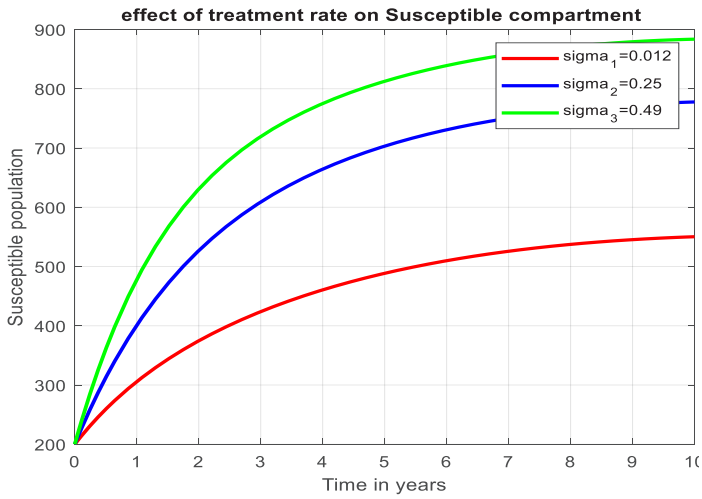

Figure 10: Effect of treatment rate on Susceptible population

As it is shown in Figure 10, increasing treatment rate of infective population leads to increment of number of susceptible populations. This shows that number of susceptible populations is directly proportional to treatment rate.

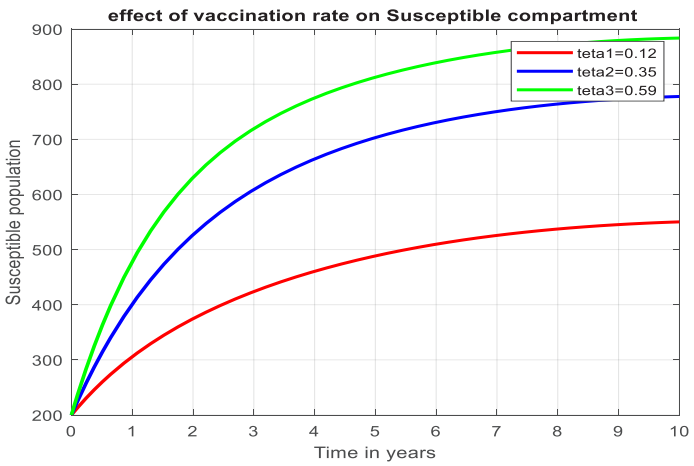

Figure 11: Effect of vaccination rate on susceptible population

From Figure 11, it is shown that as vaccination rate increases, the number of susceptible populations also increases. Subsequently vaccinating the population helps us in decreasing the number of infective population and in increasing susceptible population in the society.

Conclusion

In this paper, we propose an S-V-E-I- R-E model of hepatitis B virus infection with two controls: vaccination and treatment. First, we analyzed the dynamic behavior of the system for constant controls. In the constant controls case, we calculate the basic reproduction number and investigate the existence and stability of equilibria. There are two nonnegative equilibria of the system, namely, the disease-free and endemic. We see that the disease-free equilibrium which always exists and is locally asymptotically stable if $R_{Eff}<1$, and endemic equilibrium which exists and is locally asymptotically stable if $R_{Eff}>1$.

Reactivation of HBV is a common occurrence after immune suppression and can be clinically severe and result in death from acute liver failure or progressive liver disease and cirrhosis. HBV reactivation can be prevented in some instances by prophylactic use of antiviral agents. Controlled clinical trials and several subsequent meta-analyses have shown that prophylaxis with nucleoside analogs (most commonly lamivudine) decreases the incidence of HBV reactivation and the frequency of clinical hepatitis and death from HBV-associated liver injury in patients undergoing cancer chemotherapy [9, 10]. Initiating therapy once reactivation has occurred is typically done for control subjects in these trials and appears to be ineffective.

Thus, these meta-analyses clearly demonstrated that prophylactic lamivudine decreased the rate of HBV reactivation. Given the safety and tolerability of current nucleoside analogs for hepatitis B and given that prophylaxis against reactivation of hepatitis B appears to be effective, it would seem appropriate to recommend its application widely.

We have shown that vaccination and treatment strategies are crucial in decreasing infective population and in increasing susceptible population. Then, by increasing vaccination and treatment rate, it is found possible to decrease reproduction number of HBV which leads to decrement of infective population in the society. We have also shown that re-infection contributes to transmission of HBV which leads to increment of infective population in the society [11-37].

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